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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/890,229 | 11/27/2001 | Peter M. Bramley | B0192/7031 | 9395 |

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| EXAMINER | |
|---|---|
| KALLIS, RUSSELL | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1638 | |

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/890,229 | BRAMLEY ET AL. | |
| | Examiner | Art Unit | |
| | Russell Kallis | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21 and 24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election without traverse of Group I, Claims 1-21 and 24-34 in Paper No. 11/19/2003 is acknowledged.

### *Drawings*

The drawings are objected to because Figure 3 shows an alignment of DXP synthase protein sequences wherein the *Synechocystis* sequence does not match the corresponding *Synechocystis* sequence of SEQ ID NO: 1 in the sequence listing, but rather is an exact match for the *Bacillus* sequence of SEQ ID NO: 2. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

### *Claim Objections*

Claim 25 objected to because of the following informalities: In lines 3 and 4, the claim recites "the nucleic acid sequences identified in Figure 3". The claims and specification should refer to protein and nucleic acid sequences using sequence identifiers. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

Claims 1-21 and 24-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims methods of manipulating isoprenoid expression in a plant or plant cell, and plants and plant cells thereof, comprising altering DXPS activity; also further comprising transformation with a DXPS encoding polynucleotide or a functional equivalent and further claims transformation with one or more nucleic acids encoding a polypeptide that produces an isoprenoid.

Applicant describes DXP synthase protein of SEQ ID NO: 1, 2 and 3 from *Synechocystis, Bacillus* and *E. coli* respectively.

Applicant does not describe polynucleotides encoding DXP synthases, functional equivalents thereof, or nucleic acids encoding a polypeptide that produces an isoprenoid; or other DNA sequences that could be used to alter DXPS activity.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of polynucleotide sequences encoding a DXP synthase protein or functional equivalent falling within the scope of the claimed genus of polynucleotides that encode a DXP synthase protein. Applicants only describe DXP synthase protein sequences of SEQ ID NO: 1, 2, and 3. Further, Applicants fail to describe a representative number of any nucleic acid sequences encoding a polypeptide that produces an

isoprenoid. Furthermore, Applicants fail to describe structural features common to members of the claimed genera of polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for DXP synthase or isoprenoid producing protein activity, it remains unclear what features identify a DXP synthase or isoprenoid producing protein encoding polynucleotide. Since the genus of DXP synthase or isoprenoid producing protein encoding polynucleotides has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Given the failure of the DXP synthase or isoprenoid producing protein encoding polynucleotides to be adequately described, methods of their use are also inadequately described. See Written Description Guidelines, Federal Register Vol. 66 No. 4, Friday January 5, 2001 "Notices", pages 1099-1111.

Claims 1-21 and 24-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of overexpression of DXPS in *E. coli* and increased lycopene and Co8 production, does not reasonably provide enablement for manipulating or increasing ispoprenoid production in plants or other cells or organisms,other than *E. coli*, transformed with DXP synthase or any other combination of polynucleotides encoding an isoprenoid producing protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

Applicant broadly claims methods of manipulating isoprenoid expression in a plant or plant cell, and plants and plant cells thereof, comprising altering DXPS activity; also further comprising transformation with a DXPS encoding polynucleotide or a functional equivalent and further claims transformation with one or more nucleic acids encoding a polypeptide that produces an isoprenoid.

Applicant teaches bacterial overexpression of DXP synthase from *E.coli* (SEQ ID NO: 3) resulted in increased levels of lycopene, carotenoids and ubiqinone (UQ-8) (specification, pages 22-24); and transformed tomato expressing a DXP synthase from *E. coli* of SEQ ID NO: 3.

Applicant does not teach a method of manipulating or increasing isoprenoid activity in plants by altering or increasing the expression of any DXP synthase and by further transformation with other nucleic acids encoding a protein that produces an isoprenoid in any organism or cell other than *E. coli*; or other methods of altering DXPS activity other than overexpression of DXPS in tomato and *E. coli.*

The state of the art for isolating DNAs of defined function is highly unpredictable. Isolating DNA fragments using stringent hybridization conditions, does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40: 857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating highly stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at $65^0$C (page 859, left column, $2^{nd}$ paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2).

Furthermore, the isolation of DNA sequences that would encode the same activity from other sources introduces an element of unpredictability. The limitation is introduced in finding homologous regions that would adequately enable either PCR amplification or southern hybridization and would entail using either degenerate primers or probes with limited homology. Thus the screen for sequences with the same activity would isolate many genes other than those of interest. The inherent unpredictability in isolation of a homologous sequence encoding the same protein activity is illustrated in an example where a small number of changes to the coding region for a strict desaturase resulted in an enzyme with a hydroxylase activity and that a small number of changes to the coding region of a desaturase could account for the functional

divergence seen across a range of fatty acid metabolism enzymes (Broun P. *et al.* Science Vol. 282; 13 November 1998, pp. 1315-1317; Abstract lines 4-6 and p. 1317 column 1, lines 37-56).

Further, the phenotypic character expected from expression of a DNA construct often cannot be reliably predicted. In an example that demonstrates this all too common and unpredictable feature in the art, antisense expression of a polygalacturonase gene in transgenic tomato had no effect on fruit softening (Smith C. *et al.*; Nature 334: 724-726, 1988, p. 725).

Moreover, seed specific expression of a bacterial phytoene synthase in the seeds of *Brassica napus* did not increase all isoprenoid compounds. Although phytoene synthase levels were increased and were correlated with overall increases in carotenoids, chlorophyll levels and tocopherol levels were decreased. Thus, there are other unknown mechanisms or effects in plants that would limit increases in levels of specific isoprenoids when attempting to engineer enhanced expression of an isoprenoid. (Shewmaker C. *et al.* The Plant Journal, 1999, Vol. 20; No. 4, pages 401-412; see abstract and column 2, page 406).

Although one of skill in the art can readily isolate DNA sequences and make transformed plants one would not know based upon Applicant's disclosure which embodiments would be operable, and thus undue trial and error experimentation would be needed by one skilled in the art to make and clone a multitude of non-exemplified DXP synthase and isoprenoid producing nucleic acid sequences and would require one of skill in the art to test in a myriad of non-exemplified plants or bacteria for increased DXP synthase and the activity of some non-exemplified isoprenoid producing nucleic acid sequence to increase isoprenoid expression in a multitude of non-exemplified transformed plant species.

Given the unpredictability in the art as to which polynucleotide would encode a DXP synthase or any one of multitude of nucleic acid sequences that would encode an isoprenoid producing enzyme and which species of plant would increase production of isoprenoids when transformed with a DPX synthase and a nucleic acid encoding an isoprenoid producing enzyme; the breadth of the claims encompassing polynucleotides encoding any DXP synthase and any isoprenoid producing enzyme from any source expressed in any plant increasing any number of non-exemplified isoprenoids; the lack of guidance in the examples of the specification or in the prior art as to which nucleic acid sequences transformed into which species of plant would best serve the invention; and the undue trial and error experimentation required to practice the invention, the invention is not enabled for the scope set forth in the claims.

Claims 20-21 and 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20, "bacterial" lacks antecedence.

Claim 25, It is unclear what Applicant means since Figure 3 does not contain any nucleic acid sequences. Furthermore no nucleic acid sequences are recited in the sequence listing that encode the DXP synthase enzymes aligned in Figure 3.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 29, 33 and 34 rejected under 35 U.S.C. 101 because the claimed invention is The claimed inventions encompass untransformed plants and seeds, which are a product of nature and not one of the five classes of patentable subject matter. Claims 29, 33 and 34 are drawn to progeny and parts such as seeds and fruits of a transformed plant. Due to Mendelian inheritance of genes, a single gene introduced into a parent plant would only be transferred at most to half the male gametes and half the female gametes. This translates into only two thirds of the progeny having at least a single copy of the transgene and one quarter of the progeny would not carry a copy of the transgene. Since the claim encompasses progeny and parts such as seeds and fruits that lack the transgene, the claim encompasses plants, seeds and fruits that are indistinguishable from plants, seeds and fruits that would occur in nature. directed to non-statutory subject matter. The claims are drawn to a distinguishing phenotype i.e. a progeny plant, a fruit, or a seed having increased isoprenoid activity. This is insufficient to characterize a transformed plant, seed, or fruit. See American Wood v. Fiber Distintegrating Co., 90 U.S. 566 (1974), American Fruit Growers v. Brogdex Co., 283 U.S. 2 (1931), Funk Brothers Seed Co. v. Kalo Inoculant Co., 33 U.S. 127 (1948), Diamond v. Chakrabarty, 206 USPQ 193 (1980).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24-25 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Lange B. *et al.* PNAS March 3, 1998; Vol. 95, No. 5; pages 2100-2104.

The reference teaches overexpression in *E. coli* of a DXP synthase gene from *E. coli* wherein a start codon i.e. methionine is inherently taught, increased DXP synthase activity in transformed *E. coli* cells (see page 2103, column 2; in Results and Discussion); and the dxp synthase sequence of SEQ ID NO: 3 from *E. coli* on page 2102. Thus the reference teaches all the limitations of Claims 24-25 and 29.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15, 18, 21, 24-27 and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burkhardt P. *et al.,* The Plant Journal, 1997; Vol. 105, No. 5; pages 1071-1078; in view in view of Lange B. *et al.* PNAS March 3, 1998; Vol. 95, No. 5; pages 2100-2104.

Applicant broadly claims organisms; plant cells, plants, and cells transformed with a DXP synthase and another nucleic acid encoding an enzyme that produces isoprenoids.

Burkhardt teaches transformation of rice by transformation via microprojectile bombardment using the full length daffodil *psy* gene operably linked to the CaMV 35S promoter; expression of the daffodil phytoene synthase in rice seeds including the amyloplast transit peptide under control of the endosperm specific rice glutelin promoter (Gt1) and the accumulation of nutritionally beneficial phytoene in rice endosperm (see Abstract and see page 1072, column 2, production of transgenic plants).

Burkhardt does not teach overexpression a DXP synthase gene in a plant.

The teachings of Lange are discussed supra.

It would have been obvious at the time of Applicant's invention to modify the invention of Burkhardt to include overexpression of a DXP synthase gene encoding nucleic acid sequence from *E. coli*. One of skill in the art would have been motivated by the teachings of Lange that the mevalonate-independent pathway presents a unique opportunity for isoprenoid expression in bacteria and plants (see page 2104, column 1) and the success of Burkhardt in enhancing the expression of isoprenoids in rice by transformation with a nucleic acid encoding an isoprenoid producing enzyme i.e. phytoene synthase, and that one would have had a reasonable expectation of success of expressing genes in transformed plants and in plant and bacterial cells, wherein the choice of an endogenous or exogenous gene for genetically engineering an organism for increased isoprenoid expression is an obvious optimization of design parameters.

All claims are rejected.

Claims 16-17, 19-20, 28 and 32-34 are declared free of the prior art given the failure of the prior art to teach or reasonably suggest a transgenic tomato plant or a bactrerial, yeast or fungal cell transformed with the *E. coli* DXP synthase encoding nucleic acid of SEQ ID NO: 3 and another isoprenoid producing enzyme having a higher level of isoprenoids.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 4, 2004

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